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Yvette Alvarez-Perez 12/22/03

Yvette Alvarez-Perez Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/608,520
Applicant	:	Matthias Gerlach et al.
Filed	:	June 27, 2003
Title	:	ARYL-AND HETEROARYLCARBONYLIPERAZINES AND THEIR USE FOR THE TREATMENT OF BENIGN AND MALIGNANT ONCOSES
Attorney Docket No.	:	103832-506-NP

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SUBMISSION OF ENGLISH TRANSLATION OF PROVISIONAL APPLICATION UNDER 37 CFR 1.78(a)(5)

Sir:

The above-identified patent application claims priority from Provisional Application No. 60/393,027 filed on June 29, 2002 under 35 U.S.C. 119(e). The Provisional Application was filed in a German. Applicants submit herewith an English translation of the non-English provisional application and a statement that the translation is accurate under 37 CFR 1.78(a)(5).

The Commissioner is authorized to charge any required fees to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicants,

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Provisional Application No. 60/393,027

Title: Arylcarbonylpiperazines and heteroarylcarbonylpiperazines, and their use for the treatment of benign and malignant tumor diseases

Job No.: 6515-96120
Translated from German by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

Provisional Application

Title: Arylcarbonylpiperazines and heteroarylcarbonylpiperazines, and their use for the treatment of benign and malignant tumor diseases

Description of the invention

A dramatic increase in tumor diseases and tumor-related deaths is expected worldwide over the next few years. In 2001, worldwide, approximately 10 million people were afflicted with cancer and more than 6 million people died from this disease. The development of tumors is a fundamental disease of higher organisms in the plant and animal kingdom and among humans. The generally recognized multistep model for the formation of cancer assumes that, as a result of the accumulation of several mutations in an individual cell, this cell is changed in such a way in terms of its proliferation and differentiation characteristics that a malignant state is ultimately reached, via a benign intermediate stage, as a result of metastasis. The term cancer or tumor encompasses a disease state involving more than 200 different individual diseases. Tumor diseases can progress in a benign or malignant manner. The most important tumors are those of the lung, breast, stomach, cervix, prostate, head and neck, large intestine and rectum, liver, and the blood system. There are large differences in regard to the progression, prognosis, and therapy characteristics. More than 90% of recognized cases relate to solid tumors that are difficult to treat or are untreatable, especially in advanced stage or in the case of metastasis. The three pillars of combating cancer are still operative removal, radiation therapy, and chemotherapy. Despite great advances, it still has not been possible to develop medications successfully that bring about a distinct prolongation of survival rate or even complete healing in the case of widespread solid tumors. It is therefore useful to discover new drugs for combating cancerous disease.

Aryl and heteroaryl-substituted piperazinylcarbonyl derivatives find a multiplicity of uses as pharmacologically active compounds and as synthesis building blocks in pharmaceutical chemistry.

For example, substituted and unsubstituted acridinecarbonylpiperazides, quinolinecarbonylpiperazides and pyridinecarbonylpiperazides with anticarcinogenic properties are described in the patent specifications WO2002008194, WO2002008192, and WO2002008190 by Zentaris AG. Quinolinecarbonylpiperazides with CNS activity are mentioned in the article by A. Stanczak et al. in Pharmazie 1997, 52, 91-97. Tumor activity is neither described nor suggested. Isoquinoline derivatives and their use as local anesthetics are described by F. Duro et al. in Farmaco, 1981, 36(6), 400-411. Pyrimidines of the aforementioned type of substance with extremely varied biological properties are documented in the literature such as, for example, antilipid peroxidation activities (A. Kuno et al. in Chem. Pharm. Bull. 1992, 40,

2423-2431), or as CRF antagonists (P.J. Gilligan et al. Bioorg. Med. Chem. 1997, 7, 2321). Tumor activity for the aforementioned cases is neither described nor suggested. Pyrazines or quinoxalines are described as potential diuretics (T. Russ et al. in Arch. Pharm. 1992, 325 (12), 761), and as anthelmintic agents (R. Dubey et al. in J. Med. Chem. 1985, 28, 1748), or as HIV-1 reverse transcriptase inhibitors (D.L. Romero et al. in J. Med. Chem. 1994, 37, 999). Tumor activity for the aforementioned cases is neither described nor suggested.

Surprisingly, cytotoxic activity in different cellular models has now been demonstrated with the compounds in accordance with the invention. Moreover, it has been possible to show that, in particular, the heteroarylcarbonylpiperazines of structure I are potent inhibitors of the polymerization of tubulin.

This makes the compounds in accordance with the invention suitable for use as drugs for the treatment of benign and malignant tumor diseases in humans and animals.

The compounds in accordance with the invention can be used as a single substance or in combination with additional cytotoxic substances, such as e.g. cisplatin, carboplatin, doxorubicin, ifosfamide, cyclophosphamide, 5-FU, methotrexate, and especially in combination with signal transduction inhibitors, such as e.g. Herceptin, Glivec, or Iressa.

The medicinal drugs in accordance with the invention can be administered as liquid, semisolid, and solid forms of medication. This takes place in a way that is suitable in each case in the form of aerosols, powders and dusting powders, tablets, sugar-coated pills, emulsions, foams, solutions, suspensions, gels, ointments, pastes, pills, pastilles, capsules, or suppositories.

The medicinal drugs in accordance with the invention can be administered in a suitable form of medication as follows: on the skin, namely epicutaneously as a solution, suspension, emulsion, foam, ointment, paste, or patch; via the mucosa of the mouth and tongue, namely buccally, lingually, or sublingually as tablets, pastilles, sugar-coated pills, a linctus, or liquid for gargling; via the mucosa of the stomach and intestine, namely enterally as tablets, sugar-coated pills, capsules, solutions, suspensions or emulsions; via the mucosa of the rectum, namely rectally as a suppository, rectal capsule, or ointment; via the mucosa of the nose, namely nasally as drops, ointments, or a spray; via the bronchial and alveolar epithelia, namely in a pulmonary manner or by inhalation as an aerosol or inhalant; via the conjunctiva, namely conjunctivally as eyedrops, an eye ointment, eye tablets, lamellae, or an eye rinse; via the mucosa of the genital organs, namely intravaginally as spherical vaginal inserts, ointments and a rinsing solution, and in an intrauterine manner as uterine pessaries; via the drainage urinary tract, namely intraurethrally as a rinsing solution, ointment, or medicinal swab; into an artery, namely intraarterially as an injection; into a vein, namely intravenously as an injection or by infusion; into the skin, namely intracutaneously as an injection or implant; under the skin, namely subcutaneously as an injection or implant; into the muscle, namely intramuscularly as an

injection or implant; and into the abdominal cavity, namely intraperitoneally as an injection or infusion.

The invention additionally comprises processes for the synthesis of the compounds of structure I in accordance with the invention.

If the compounds of general formula I in accordance with the invention have at least one center of asymmetry, then they can be present in the form of their racemates, or in the form of pure enantiomers and/or diastereomers, or in the form of mixtures of these enantiomers and/or diastereomers, namely as the substance and also as pharmaceutically acceptable salts of these compounds. The mixtures can be present in any desired ratio in which the stereoisomers are mixed.

If possible, the compounds in accordance with the invention can be present in the form of tautomers.

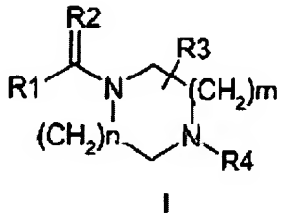
The compounds of general formula I in accordance with the invention can be transformed into salts using inorganic and organic acids provided that they possess an adequately basic group, such as e.g. a secondary or tertiary amine. The pharmaceutically acceptable salts of the compounds of general formula I in accordance with the invention are preferably formed using hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid, carbonic acid, formic acid, acetic acid, trifluoroacetic acid, oxalic acid, malonic acid, maleic acid, succinic acid, tartaric acid, racemic tartaric acid, malic acid, embonic acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, or aspartic acid. The salts that are formed are, inter alia, hydrochlorides, hydrobromides, sulfates, phosphates, methanesulfonates, sulfoacetic acid hydrate, tosylates, carbonates, hydrogen carbonates, formates, acetates, triflates, oxalates, malonates, maleates, succinates, tartrates, malates, embonates, mandelates, fumarates, lactates, citrates, and glutamates. The stoichiometry of the salts that are formed from the compounds in accordance with the invention can hereby amount to integral or nonintegral multiples of one.

The compounds of general formula I in accordance with the invention can be transformed into their physiologically acceptable salts using inorganic and organic bases provided that they contain an adequately acidic group, such as e.g. the carboxy group. The following can be considered as inorganic bases: sodium hydroxide, potassium hydroxide, calcium hydroxide; and the following can be considered as organic bases: ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dibenzylethylenediamine, and lysine. The stoichiometry of the salts that are formed from the compounds in accordance with the invention can hereby amount to integral or non-integral multiples of one.

Solvates are also preferred, especially the hydrates of the compounds in accordance with the invention that can be obtained by e.g. crystallization from a solvent or from an aqueous

solution. One, two, or three solvate or water molecules, or as many as thereof desired, can hereby combine with the compounds in accordance with the invention to give solvates and hydrates.

General formula I in accordance with the claim:



I

R1: thiophene, phenazine, fluoren-9-one, isoxazole, oxazole, thiadiazole, 1,2,3,4-tetrahydroquinoline, 1H-pyrrole, indole, quinoline, isothiazole, quinoxaline, isoquinoline, biphenylene, 9H-fluorene, 9H-xanthene, anthraquinone, 1H-pyrazole, furan, 1H-indazole, xanthen-9-one, chromen-4-one, 10,10-dioxo-10H-10λ^6-thioxanthen-9-one, pyrimidine, 2,3-dihydrobenzo[1,4]dioxin, benzofuran, benzothiazole, 9H-carbazole, benzimidazole, imidazo[1,2-a]quinoline, imidazo[1,2-a]pyridine, azulene, dibenzofuran, thianthrene, 10H-phenothiazine, whereby the heteroaromatic or aromatic groups can be substituted or unsubstituted;

R2: O, S, NH, NR5;

R3: represents one or up to 16 substituents selected from the following group: H, unsubstituted or substituted alkyl, halogen, COOH, $CONH_2$, whereby the substituents can be arranged vicinally or geminally on the heterocycle;

R4: unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, unsubstituted or substituted alkylaryl, unsubstituted or substituted alkylhet[ero]aryl;

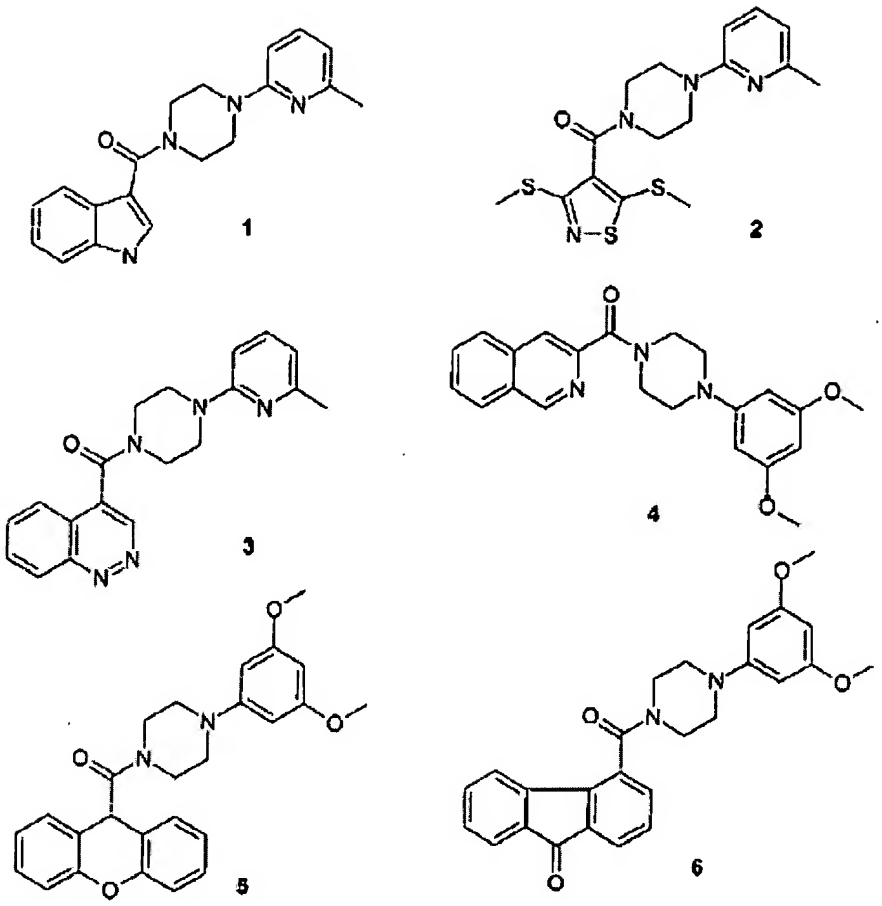
R5: unsubstituted or substituted alkyl, unsubstituted or substituted alkylaryl, unsubstituted or substituted alkylheteroaryl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl, hydroxyl, NH_2, NHR6 or OR7;

R6, R7: unsubstituted or substituted alkyl, unsubstituted or substituted alkylaryl, unsubstituted or substituted alkylheteroaryl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaryl;

m, n: 0-3.

In all cases, the alkyl residue can signify [sic; be] branched or unbranched, and saturated or unsaturated.

Embodiment examples:



Biological data:
Inhibition of tubulin polymerization (bovine tubulin, 30% MAPS):

(1) Verbindung	IC50 [µM]
5	2.53
6	2.31

Key: 1 Compound

Inhibition of selected tumor cell lines:

Verbindung (1)	KB/HeLa IC50[µM]	NCI-H460 IC50[µM]	RKOP27 IC50[µM]	SF-268 IC50[µM]	SK-OV-3 IC50[µM]
5	0.19	0.19	0.14	0.17	0.07
6	0.43	0.52	0.40	0.39	0.25

Key: 1 Compound